Differential Effect of a Drug

by

Somesh Das Gupta
University of Minnesota and
Indian Statistical Institute

Technical Report No. 467
March 1986

1. Introduction

The effect of a drug is generally tested by the paired t-test under normality assumption. However, such a test cannot assess whether the drug has any "differential effect," i.e. whether the effect of the drug changes with the baseline value. It should be noted that the paired t-test simply judges the overall effect (like the main effect) whereas the differential effect is some sort of interaction, and the presence of one effect does not necessarily imply the presence of the other.

In a recent paper Berry et al (1984) formulated the problem of assessing the presence of the differential effect. Let X_1 be the baseline observation and X_2 be the observation after the administration of the drug. Berry et al (1984) assumed that

$$\binom{X_1}{X_2} \sim N_2\left[\binom{\mu}{\mu+\Delta},\ \begin{pmatrix}\sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2\end{pmatrix}\right],$$

and they argued that even when the drug had no effect, i.e., $\Delta = 0_1\sigma_1 = \sigma_2$, the presence of the differential effect might be falsely ascertained from the regression coefficient of X_2-X_1 on X_1 as given below:

$$E[X_2-X_1|X_1] = -(1-\rho)(X_1-\mu).$$

So, in order to assess the differential effect of the drug, Berry et al (1984) suggested to study the linear regression of the residual $Y = (X_2-X_1) +$

$(1-\rho)(X_1-\mu)$ on X_1 as given below:

$$E(Y|X_1) = \Delta + \rho(\theta-1)(X_1-\mu),$$

where $\theta = \sigma_2|\sigma_1$. Now, according to Berry et al (1984), the absence of the differential effect can be judged by testing $\theta = 1$, and a differential effect, if present, is positive or negative corresponding to the sign of $\rho(\theta-1)$. The test for $\theta = 1$ is the well-known Pitman-Morgan test.

The purpose of this note is to indicate that the problem of assessing the differential effect of the drug has not been correctly posed in the paper by Berry et al (1984). Even in their model the effect of the drug and the differential effect, in particular, may be reflected through ρ as well. They are confused between ρ and the autocorrelation which one would get through repeated measurements on the patients without application of the drug.

2. The Model and Assessment of the Differential Effect

Consider the following set-up:

$$\begin{aligned} X_1 &= U + e_1, \\ X_1' &= U + e_1', \\ X_2 &= a + bU + e_2, \end{aligned}$$

where X_1 and X_1' are two independent measurements of the "true" (averaged over time or errors of measurements) base-line value U at two given points of time without any application of the drug, and X_2 is the observation after the application of the drug at the same time-point as that of X_1' (so that time points do not blur the issue). The variable U refers to the baseline value of a patient in a given population. It is assumed that $E(e_1) = E(e_1') = E(e_2) = 0$, and e_1, e_1', e_2 and U are mutually independent. So, in terms of the above model,

$$\sigma_1^2 = \sigma_u^2 + \sigma^2 , \quad \sigma_2^2 = b^2\sigma_u^2 + \eta^2 , \quad \rho\sigma_1\sigma_2 = b\sigma_u^2 ,$$

where $\sigma_u^2 = \mathrm{Var}(U)$, $\sigma^2 = \mathrm{Var}(e_1)$, $\eta^2 = \mathrm{Var}(e_2)$. On the other hand

$$\mathrm{Var}(X_1) = \mathrm{Var}(X_1') = \sigma_u^2+\sigma^2, \quad \mathrm{Cov}(X_1,X_1') = \sigma_u^2,$$

assuming $\mathrm{Var}(e_1') = \sigma^2$.

The differential effect of the drug, represented by the factor b, is reflected in the variance of X_2, as well as in the correlation between X_1 and X_2. The "intrinsic" correlation between X_1 and X_1' is given by

$$\tilde{\rho} = \sigma_u^2/(\sigma_u^2+\sigma^2),$$

whereas the correlation between X_1 and X_2 is

$$\rho = (b\sigma_u^2)(\sigma_u^2+\sigma^2)^{-1/2}(b^2\sigma_u^2+\eta^2)^{-1/2}.$$

It may be noted that ρ is an increasing function of b, when all other parameters are fixed. When $\eta^2 = \sigma^2$,

$$\sigma_{11} = \sigma_{22} \Leftrightarrow b^2 = 1, \quad \text{and} \quad b = 1 \Leftrightarrow \sigma_{11} = \sigma_{22}, \sigma_{12} > 0.$$

On the other hand, under $\eta^2 = \sigma^2$

$$b = 1 \Leftrightarrow \rho = \tilde{\rho}.$$

The linear regression of X_2-X_1 on X_1 under b = 1 is given by

$$(a+b\mu-\mu) - (1-\tilde{\rho})(X_1-\mu),$$

where $E(U) = \mu$. Define the residual by

$$Z = (X_2-X_1) + (1-\tilde{\rho})(X_1-\mu).$$

Then the linear regression of Z on X_1, under the general model is given by

$$\tilde{a} + \tilde{\rho}(b-1)(X_1-\mu),$$

where

$$\tilde{a} = a + b\mu - \mu.$$

Thus the regression coefficient of Z on X_1 is zero if, and only if, $b = 1$. We have already noted that $b = 1$ is not equivalent to $\sigma_{11} = \sigma_{22}$ even when $\sigma^2 = \eta^2$.

Berry et al. (1984) did not notice that ρ might contain the influence of the differential drug effect. They assumed $\rho = \tilde{\rho}$ and derived a wrong formula for the residual Z. Thus the Pitman-Morgan test, suggested by Berry et al. (1984) for testing the nullity of the differential drug effect, does in fact test the hypothesis $b = \pm 1$.

The measure of the differential effect is not clearly stated in Berry et al. (1984); on the other hand, they pointed out that the differential effect would be positive or negative according to the sign of $\rho(\theta-1)$, where $\theta = \sigma_2/\sigma_1$. However, in our formulation of the problem

$$\mathrm{sign}[(\theta-1)\rho] = \mathrm{sign}[(b^2-1)b],$$

and $\mathrm{sign}[(b^2-1)b]$ is positive even when $-1 < b < 0$! Now note that the regression coefficient of Z on X is $\tilde{\rho}(b-1)$, which is positive or negative according as b is greater or less than 1.

3. Test for the Differential Effect

Suppose that X and Y are distributed according to a bivariate normal distribution. When $\sigma^2 = \eta^2$, a confidence region of confidence coefficient $1 - \alpha$

may be obtained from

$$\frac{\sqrt{n-2}\,|r_b|}{\sqrt{1-r_b^2}} \le t_{n-2}^{\alpha/2},$$

where $t_{n-2}^{\alpha/2}$ is the upper $(\alpha/2)$-fractile of Student's t-distribution with n-2 degrees of freedom, and r_b is the sample correlation coefficient between X_2-bX_1 and bX_2+X_1. The above procedure includes the Pitman-Morgan test, in particular. However, this confidence region seems to be inadequate, since $r_b = -r_{(-1/b)}$.

When $\sigma^2 = \eta^2$, the nullity of the differential effect (i.e., $b = 1$) can be ascertained by a large sample test of $\rho = \tilde{\rho}$, based on independent observations on (X_1,X_1') and separate independent observations on (X_1,X_2). (See Anderson (1958)).

Next, note that the maximum likelihood estimate of b under $\sigma^2 = \eta^2$ is given by

$$\hat{b} = \frac{2S_{12}}{-(S_{22}-S_{11}) + [(S_{22}-S_{11})^2+4S_{12}^2]^{1/2}},$$

where

$$\begin{pmatrix} S_{11} & S_{12} \\ S_{12} & S_{22} \end{pmatrix}$$

is the sample covariance matrix of X_1 and X_2. It can be shown (from Anderson (1958)) that, under $b = 1$, $\sqrt{n}(\hat{b}-1)$ is asymptotically distributed as the normal distribution with zero mean and variance $(1-\rho^2)/\rho^2$, as $n \longrightarrow \infty$. Hence, a large-sample test of $b = 1$ can be devised by using the statistic

$$\sqrt{n}(\hat{b}-1)[(1-\hat{\rho}^2)/\hat{\rho}^2]^{-1/2},$$

where $\hat{\rho}$ is a consistent estimate of ρ.

In the nonparametric set-up, one may consider the permutational distribution of n observations on (X_1,X_2) by permuting X_1,X_2 in each pair; one may then consider the correlation between X_1 and X_2 as a test statistic.

Note: When $\sigma^2 \neq \eta^2$, the parameter b is not well-determined. As a matter of fact, $\sigma_{11} = \sigma_{22}$ when

$$(1-b^2)\sigma_u^2 = \eta^2 - \sigma^2,$$

and $\tilde{\rho} = \rho$ when

$$\eta^2 = b^2\sigma^2, \quad b > 0.$$

References

1. Anderson, T.W. (1958). An Introduction to Multivariate Statistical Analysis. Wiley, New York.

2. Berry, D.A., Eaton, M.L., Ekholm, B.P., Fox, T.L. (1984). Assessing Differential Drug Effect. Biometrics, 40, 1109-1115.

3. Puri, M.L., Sen, P.K. (1971). Nonparametric Methods in Multivariate Analysis. Wiley, New York.